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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,049	01/17/2006	Kristen E. Belmonte	PU60400	6150

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SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,049	BELMONTE ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2X 25 June 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

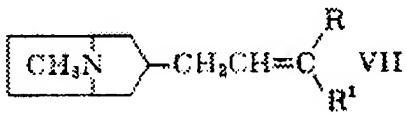
DETAILED ACTION

1. Claims 1-4 and 6-15 are pending in the application.

2. This application is a national stage of PCT/US2004/023042 filed on July 16, 2004 which claims priority to U.S. Provisional Application No. 60/488,061 filed July 17, 2003.

Response to Arguments

3. Applicant's arguments filed on have been fully considered but they are not persuasive. With respect to the 102 rejection, on the compounds of Zirkle, As per pg. 349 paragraph 2 "The tropane alkane derivatives listed in Table IV were obtained by reduction of the corresponding olefins. Olefin VII was hydrogenated smoothly over Raney nickel at room temperature and 4.2 kg./cm hydrogen pressure....." Compound VII is the olefin:



The relative portion of Table IV is reproduced here:

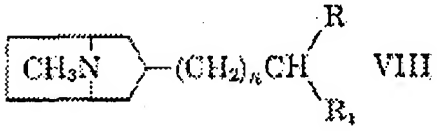
352 ZIRKLE, ANDERSON, CRAIG, GERNS, INDIK, AND PAVLOFF Vol. 5

TABLE IV
3-SUBSTITUTED TROPANE ALKANES

Compound[a] No.	n	R	R'	Config.	Salt	M.p., °C.	Solvent[d]
a	0	CH_3	CH_3	α[b]	...	...[c]	
					HCl	194–196	AB
					CH_3I	224–226	AB
b	0	C_6H_5	C_6H_5	α[b]	...	70–72	
					HCl	>310	AB
					CH_3Br	277–278	CA
c	1	C_6H_5	C_6H_5	α	HCl	244–245	AB
					CH_3Br	257–258	AB

It would appear that structure VIII was omitted from the top heading of Table IV.

March 1962 3-Substituted Tropane Derivatives. III 353



VIII

The thrust of the argument seems to be that the reference is not enabled. Clearly these compounds are simply salts of the free amines, and this operation (mixing with acid or alkyl halide/crystallizing) was not discussed in detail. It is relatively common for scientists not to discuss trivial procedures that all in the art are aware. This reaction of amines has been known for a very long time, for example a 1924 introductory lab text where the hydrochloride salt of methyl amine is prepared (Norris, James F. *Experimental Organic Chemistry* McGraw-Hill: New York, 1924, pgs. 88-91.) Arguing the enablement of Zirkle is even more surprising since the specification itself relies on Zirkle (also cited on the IDS) pg 5 reproduced here:

METHODS OF PREPARATION

The compounds of Formula (I) may be obtained by applying synthetic procedures well known in the art as described in the patent US2800478 incorporated herein in its entirety by reference.

SYNTHETIC EXAMPLES

The above synthetic examples in this invention are referenced to the examples described in the patent US2800478, incorporated herein in its entirety by reference.

The relevant portion of Zirkle U.S. patent 2,800,478 is reproduced below:

nium hydroxide solution. The ether layer is separated and the solvent evaporated to give 1,1-diphenyl-2-(3-tropane)ethylene as a white crystalline solid which melts at 109.5–110° C. after recrystallization from acetone.

1,1-diphenyl-2-(3-tropane)ethane.—10 grams of 1,1-diphenyl-2-(3-tropane)ethylene dissolved in ethanol is hydrogenated over Raney nickel at 500 p. s. i. and 60° C. until hydrogen absorption ceases. After removal of the catalyst and evaporation of the solvent 1,1-diphenyl-2-(3-tropane)ethane is obtained as a colorless oil.

The hydrochloride of the base, formed in ethereal hydrogen chloride solution, melts at 244–245° C. after recrystallization from a mixture of ethanol and ether.

1,1-diphenyl-2-(3-tropane)ethane methobromide.—By allowing a mixture of 1 gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methylbromide dissolved in acetone to stand at room temperature for several hours, the methobromide salt is obtained as white crystals. The product, after recrystallization from a mixture of ethanol and ether, melts at 257–258° C.

1,1-diphenyl-2-(3-tropane)ethane metho-p-toluenesulfonate.—An acetone solution of one gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methyl p-toluenesulfonate is heated at reflux temperature for five minutes. By addition of ether to the cooled solution the quaternary ammonium salt is precipitated as a white solid.

1,1-diphenyl-2-(3-tropane)ethane maleate.—By adding 0.12 g. of maleic acid to 0.30 g. of 1,1-diphenyl-2-(3-tropane)ethane dissolved in ethanol and evaporating the resulting solution to dryness in vacuo the maleate salt of the base is obtained.

The implication here is that applicant is arguing that the instant specification is not enabled. Clearly the applicant is aware of the work of Zirkle, unless the argument is that Zirkle could at one time prepare the compounds (in the U.S. patent) and then later was unable to prepare them (in *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356.). This admission could form the basis of an enablement rejection. Regardless the claims have now been amended to cover not compounds but compositions, and thus an appropriate rejection under 35 U.S.C. 102 will be made based on these amendments (claims 1-4). Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or

she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

Rejecitons of claim 5 are withdrawn.

The enablement rejection is maintained for the reasons of record with some discussion below.

Objections to the specification are withdrawn.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Zirkle et. al. U.S. patent 2,800,478. Zirkle teaches the compounds of the current invention invention as a solution in ethanol. In this publication the compound of claim 3 (3-endo)-3-(2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide (applicant's name), Registry #: 106655-97-4 is synthesized and evaluated for its anticholinergic activity. The examiner believes this reference to be clearly enabled. Clearly ethanol solutions of these compounds can be inhaled or taken orally. They were hydrogenated in ethanol, and also recrystallized form ethanol or ethanol/ether

nium hydroxide solution. The ether layer is separated and the solvent evaporated to give 1,1-diphenyl-2-(3-tropane)ethylene as a white crystalline solid which melts at 109.5–110° C. after recrystallization from acetone.

1,1-diphenyl-2-(3-tropane)ethane.—10 grams of 1,1-diphenyl-2-(3-tropane)ethylene dissolved in ethanol is hydrogenated over Raney nickel at 500 p. s. i. and 60° C. until hydrogen absorption ceases. After removal of the catalyst and evaporation of the solvent 1,1-diphenyl-2-(3-tropane)ethane is obtained as a colorless oil.

The hydrochloride of the base, formed in ethereal hydrogen chloride solution, melts at 244–245° C. after recrystallization from a mixture of ethanol and ether.

1,1-diphenyl-2-(3-tropane)ethane methobromide.—By allowing a mixture of 1 gram of 1,1-diphenyl-2-(3-tropane)ethane and excess methylbromide dissolved in acetone to stand at room temperature for several hours, the methobromide salt is obtained as white crystals. The product, after recrystallization from a mixture of ethanol and ether, melts at 257–258° C.

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1,1-diphenyl-2-(3-tropane)ethane maleate.—By adding 0.12 g. of maleic acid to 0.30 g. of 1,1-diphenyl-2-(3-tropane)ethane dissolved in ethanol and evaporating the resulting solution to dryness in vacuo the maleate salt of the base is obtained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of claims 6-15 under 35 U.S.C. 112, first paragraph, is maintainted (or newly stated for the fresh claims 14-15) as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)

(A) The breadth of the claims: The claims are broad and drawn to many conditions, respiratory and otherwise but that's not really the main concern here, the main concern its that these compounds have not been shown to be useful for treating any disease. **(B) The nature of the invention:** This invention is drawn towards a method for treating diseases. **(D) The level of one of ordinary skill:** One of ordinary skill in the art of treating diseases or determining which drug to use for the treatment of a condition would be either a medical doctor or Pharm D. **(C) The state of the prior art:** While Zirkle states that these compounds are the preferred compounds of his study, and effective *in vitro* as anti-cholinergics (ibid. pg. 352-353), we don't know how these compounds behave *in vivo*.

(F) The amount of direction provided by the inventor and (G) the existence of working examples: While the applicant has provided descriptions of assays in the specification, and statements like "All data is given as mean +- standard error of the mean..."(pg. 7), the examiner cannot find the data in the specification. Statements like the one found on pg 9 line 14 "This

experiment allows for the determination of duration of activity of the administered compound..." without actually providing a single piece of data lead the examiner to believe that these are mere recitations of possible experiments that could be performed with the compounds and that none were actually performed. No working examples exist. Its is true as the applicant has pointed out that no requirement exists for in-vivo data, however only if some clear correlation exists between the in-vitro assay and the disease state. What is the in-vitro assay? Clearly one can come up with prophetic assays, that do little to ease the unpredictable nature of these experiments as delineated below. **(E) The level of predictability in the art and (H) the quantity of experimentation needed to make or use the invention:** In the absence of this data we are left with an old compound that is an anticholinergic, however it is well known that there are many muscarinic receptor sub-types and even before the application was filed a review article (Lee, A.M. et. al. *Current Opinion in Pharmacology* **2001**, *1*, 223-229) tells us that at least five distinct subtypes of muscarinic receptor exist (M1-M5 in humans). Each one of these GPCRs has distinct tissue distribution, second-messengers and most-importantly ligand profile. All that we currently know about these compounds is that they inhibit the action of acetylcholine in a non-specific assay (given in 1962 the subtypes of muscarinic receptors were not known). Maybe these were organ bath assays with sheep vas deferens, pig heart or guinea pig ileum. We don't know, but it would be helpful to know the tissue type and animal. Even if we know the tissue type these receptors are of course GPCRs and the differences between the animal protein and those found in humans is sometimes substantial (more or less subtypes, or little homology). What creatures will be treated with these compounds? It was well known at the time of the invention that in order to be used in applicants claimed manner (a disease, and specifically a lung

disease like COPD and asthma, claims 7-12), that the sub-type selectivity is very significant parameter to be determined in assessing the *potential* therapeutic benefit of a putative pharmaceutical. Lee, A.M. et. al. ibid. state on pg. 225:

> Nonselective muscarinic receptor antagonists
> Atropine, ipratropium and oxitropium are nonselective antimuscarinic drugs that successfully abrogate bronchoconstriction and airway hyperreactivity in humans; however, they bind M2 and M3 muscarinic receptors with equal affinity [5]. Since the M2 subtype is an inhibitory prejunctional autoreceptor, blocking the M2 muscarinic receptor with a nonselective antagonist increases acetylcholine release and **may enhance bronchoconstriction.**
> Ipratropium (Boehringer Ingelheim Pharmaceuticals Inc., California, USA) is the most widely used anticholinergic medication for airway disease. In guinea pigs, although it prevents bronchoconstriction in doses above 10 μg/kg (intravenous), it doubles vagally stimulated bronchoconstriction at lower doses. [48]. Paradoxical bronchoconstriction to ipratropium has been reported in humans [49,50], although no systematic study of M2 receptor blockade has been performed. Thus, the clinical efficacy of anticholinergics probably depends on the balance between M2 and M3 muscarinic receptor antagonism.

Thus we need to know several things: 1) Do these compounds antagonize muscarinic receptor subtypes found in the lungs? 2) What is the selectivity for receptor subtypes? 3) Are the effects *in vitro* correlated with *in vivo* activity? Number three is perhaps the most important factor, given the complexity of receptor sub-types, the possibly different affinities, rates of dissociation, etc. The real question is does it work as a therapy in a creature? Again it must be reiterated that applicant has provided absolutely no data for these compounds, although Smith-Kline French may have acquired such data, it has apparently not been published. Since no data is given we cannot begin to evaluate these compounds as drugs, hence any claim directed towards inhalant

formulations cannot be evaluated. It is also noted that no such formulations have been prepared and applicant has simply listed a laundry list of possibilities. We are provided with no answers to the questions above, thus it is very clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation. In regards to claim 6 which is drawn to inhibiting binding to "a mammal in need thereof", we do not know what mammals need this compound since no physiological outcome has been associated with administering these compounds, thus no veterinarian or physician would know which mammals should receive this material.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

8. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER

RDesai
7/26/07